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(54) **PHARMACEUTICALLY ACTIVE NANOSUSPENSIONS**

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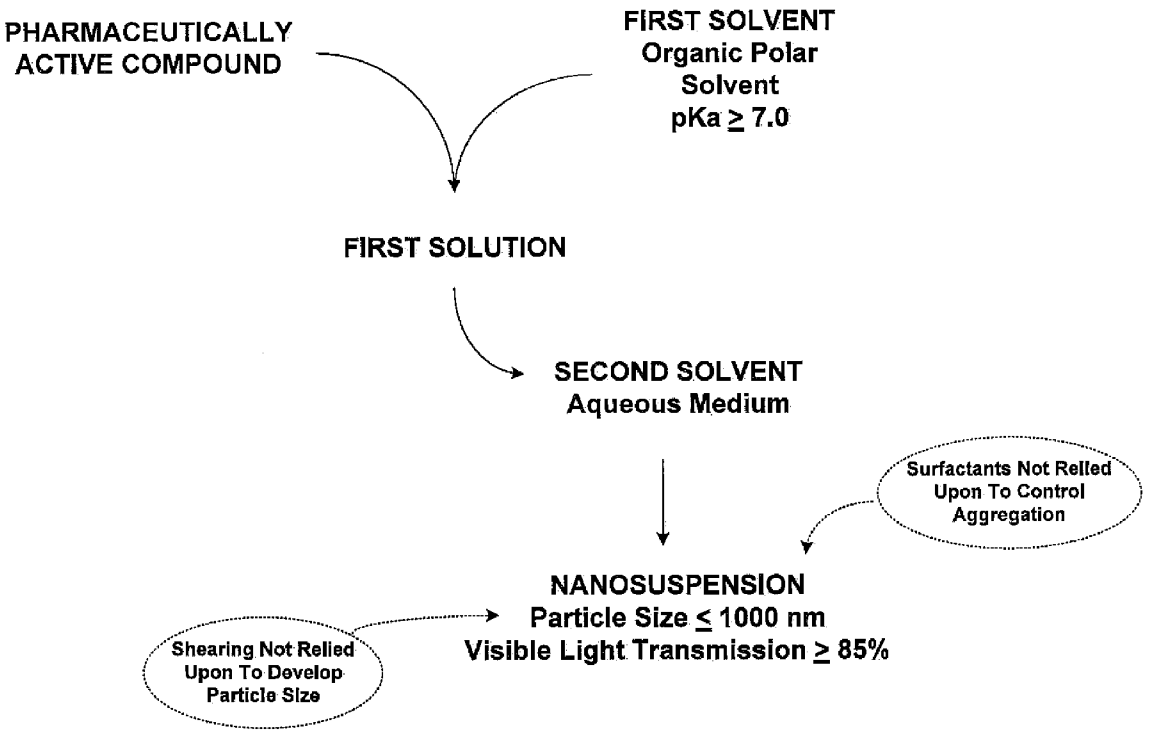
(57) **ABSTRACT**

The present disclosure is directed at a pharmaceutically active nanoparticle suspension that may be optically clear. Such suspensions may be formed by selective dissolution of a pharmaceutically active compound in a first solvent followed by introduction into a second solvent, such as an aqueous medium, without substantial use of surfactants and/or mechanical shear.



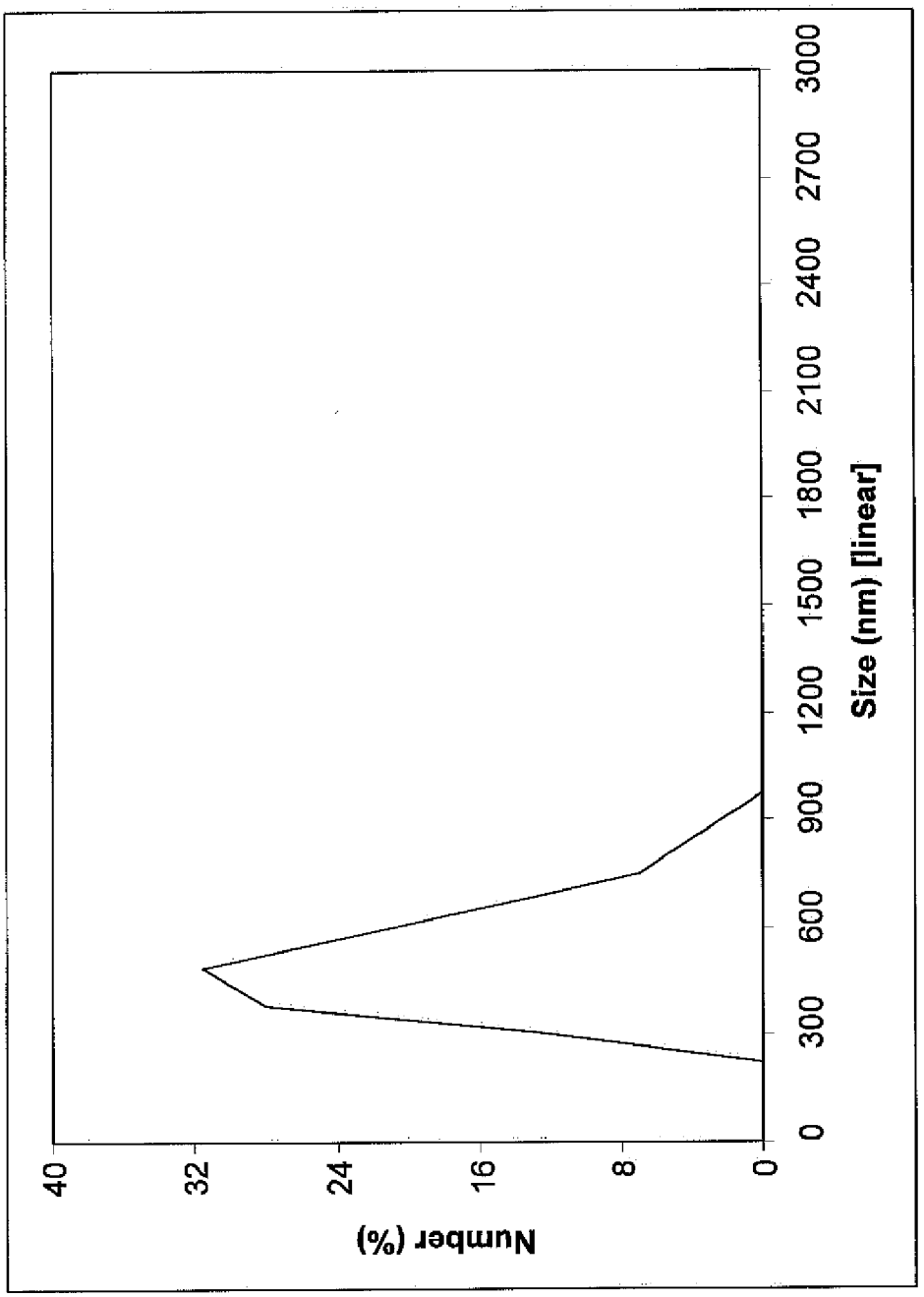

Number (%)
0
8
16
24
32
40
0
300
600
900
1200
1500
1800
2100
2400
2700
3000
Size (nm) [linear]

Figure 1

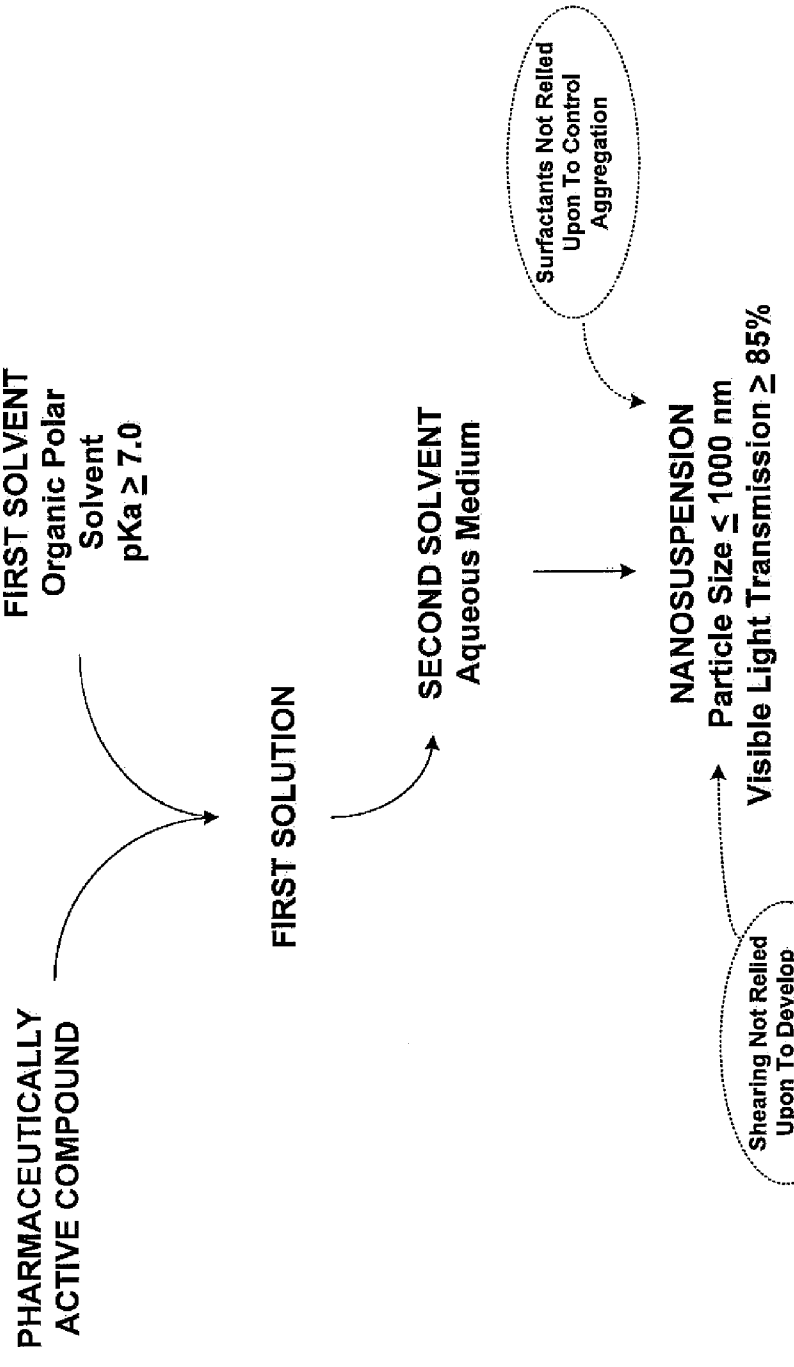

PHARMACEUTICALLY ACTIVE COMPOUND
FIRST SOLVENT Organic Polar Solvent pKa ≥ 7.0
FIRST SOLUTION
SECOND SOLVENT Aqueous Medium
NANOSUSPENSION Particle Size ≤ 1000 nm Visible Light Transmission ≥ 85%
Surfactants Not Relied Upon To Control Aggregation
Shearing Not Relied Upon To Develop Particle Size

FIG. 2

PHARMACEUTICALLY ACTIVE NANOSUSPENSIONS

FIELD OF THE INVENTION

[0001] The present disclosure relates to pharmaceutically active nanoparticle suspensions. In particular, the present disclosure relates to a process for the preparation of pharmaceutically active and optically clear nanosuspension by selective dissolution of a pharmaceutically active compound in a first solvent followed by introduction into a second solvent, such as an aqueous medium, without substantial use of surfactants and/or mechanical shear.

BACKGROUND

[0002] Pharmaceutically active compounds, such as corticosteroids, may be understood as steroids produced by the adrenal cortex. Triamcinolone (TCO) is a synthetic corticosteroid that may be used to treat certain conditions such as inflammatory response due to retinal reattachment surgery. It may also be used to treat certain forms of arthritis, skin, blood, kidney, eye, thyroid and intestinal disorders, severe allergies, and asthma. TCO may be administered orally, by injection, inhalation or as a topical cream. Triamcinolone and other assorted pharmaceutically active compounds may exhibit poor solubility in aqueous media. Poor solubility may generally be associated with poor bioavailability. Bioavailability may be understood as the rate and extent in which the pharmaceutically active compound, as a drug, is absorbed by the body in a physiologically active form. By reducing the particle size of a drug and increasing the surface area of a drug the rate of dissolution may be increased and therefore may also increase bioavailability.

SUMMARY OF THE INVENTION

[0003] In exemplary embodiment, the present disclosure provides a nanoparticulate suspension of a pharmaceutically active compound. The suspension may be formed by combining a pharmaceutically active compound in a first solvent which may then be introduced into a second solvent which may then promote active compound precipitation. The first and/or second solvents may be substantially free of surfactant. The nanoparticulate suspension may be optically clear and contain active compound particulate of a desired particle size and may also be prepared without the use of mechanical shearing.

BRIEF DESCRIPTION OF THE DRAWINGS

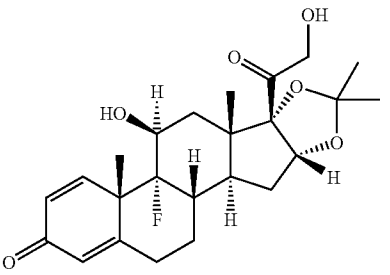
[0004] FIG. **1** illustrates one exemplary numerical particle size distribution of a nanoparticulate suspension.

[0005] FIG. **2** diagrams one exemplary method for preparation of a nanoparticulate suspension.

DETAILED DESCRIPTION

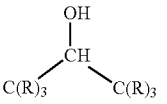
[0006] The present disclosure relates to pharmaceutically active nanoparticle suspensions. A pharmaceutically active compound may be understood herein as a compound that exhibits biological activity, including nutritional, nutraceutical and/or pharmacological activity. The nanoparticle suspensions herein are contemplated for use as an injectable formulation, such as a formulation to inhibit inflammatory response, via techniques such as intravitreal administration. The nanoparticle suspensions are also contemplated for use in general drug delivery where increased bioavailability may be desired.

[0007] The nanoparticle suspension may include, as one example of a pharmaceutically active compound, a corticosteroid. The suspension may specifically include synthetic corticosteroid such as triamcinolone (TCO) represented by the following formula:



Other corticosteroids contemplated for use herein may include betamethasone, budesonide, cortisone, dexamethasone, cortisol, methylprednisolone, prednisone, prednisolone, etc.

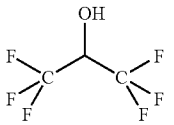
[0008] The pharmaceutically active compound may be mixed with a first solvent, such as an organic solvent, which may specifically be a relatively polar solvent and/or which may be miscible with water to provide a single homogenous phase. Reference to polar solvent may be understood as an organic solvent containing one or more chemical functional groups (e.g., a hydroxyl group) in addition to carbon and hydrogen. As one representative example, the solvent may therefore include an organic alcohol, such as a secondary organic alcohol of the following general structure:



In the above general formula, the secondary alcohol may have one or a plurality of electron withdrawing R groups associated with the carbon atom(s) adjacent the hydroxyl group, such as halogens, carbonyl groups, nitrites, etc. Accordingly, an electron withdrawing group may be understood herein as any chemical functionality which may withdraw electrons and provide a relatively more acidic alcohol. In addition, as one or more R groups may comprise an electron-withdrawing group, the remaining R groups may include a hydrogen atom, an alkyl group, an aromatic group, a substituted alkyl group or a substituted aromatic group. The polar organic solvent may also be one that exhibits hydrogen bonding and is therefore capable of dissolving molecules with hydrogen bonding receptive sites such as oxygen, double bonds or amine groups.

[0009] In addition, the organic solvent herein may be separately characterized as having an acid ionization constant (pK_a) which may be understood as the propensity of the solvent to donate a proton in water at 25° C. Such pK_a may be greater than or equal to about 7.0. The pK_a may also fall in the range of about 7.0 and 14.0, including all values and incre-

mental ranges therein, such as 9.0, 9.2, 9.4, 9.6, etc and/or 9.0-10.0, etc. One particularly suitable organic solvent may include hexafluoroisopropanol, $C_3H_2OF_6$ or HFIP, which may also be represented by the following general structural formula:



[0010] In one exemplary embodiment, the pharmaceutically active compound, such as a corticosteroid, may be present in the first solvent (Sol_1) such as HFIP at a ratio of less than about 2 mg of pharmaceutically active compound to at least 0.5 mL of HFIP, including all values and increments therein. For example, the pharmaceutically active compound may be present in the first solvent at the range of 0.001 to 1.99 mg to at least 0.5 mL of solvent, including all values and ranges therein. Accordingly, the pharmaceutically active compound may be prepared by forming a solution of about 1 mg of TCO in about 0.5 mL of HFIP. The solution of the pharmaceutically active compound and first solvent may then be added to a second solvent (Sol_2), such as an aqueous medium. It may also be appreciated that both the first solvent and/or second solvent are such that they do not substantially rely upon the use of surfactant (e.g. anionic, cationic or non-ionic surfactants) or other related compounds having both hydrophobic and hydrophilic type functionality. That is, the solvents herein, which may be characterized as being substantially free of surfactants, may be understood as solvents in which surfactants are not relied upon to control and/or avoid particle aggregation. Accordingly, the level of surfactant herein may be at or less than about 1.0 pppm.

[0011] The second solvent may include an aqueous saline solution or a buffered saline solution such as phosphate buffered saline solution. Water, such as deionized water may also be employed which may be understood as water that lacks ions but which may contain other non-ionic type compounds. The pH of the aqueous medium may also be adjusted to approximately 6.0 to 9.0, including all increments and values therein, such as 7.4, 7.3, 8.0, etc. The organic solution of the pharmaceutically active compound and first solvent (e.g., 1 mg TCO/0.5 mL HFIP) may then be added to 2 mL or greater of the aqueous medium, including all values and increments therein to provide a nanoparticulate suspension or nanosuspension (i.e. precipitation of the pharmaceutically active compound). It may now therefore be appreciated that one non-limiting aspect of the method herein contemplates the combination of a relatively smaller amount of the first organic solvent with a relatively larger amount of the second aqueous based solvent, wherein as noted above, both solvents do not rely upon surfactants to regulate the potential for precipitated particle aggregation. In addition, it may be appreciated that the foregoing method does not rely upon the use of shearing to influence particle size formation within the nanosuspension, and in particular, the shearing procedure reported in U.S. Pat. No. 5,145,684. However, it may be appreciated that the nanoparticulate suspensions herein may utilize magnetic stirrers and other related techniques of stirring/agitation.

[0012] The nanosuspension formed herein may then be concentrated. For example, it may be concentrated to a ratio of 1 mg or less of pharmaceutically active compound to 1.25 mL or greater of first solvent and aqueous medium. Concentration may be performed by removing some of the aqueous medium and/or first solvent, via placement in a fume hood or by application of vacuum.

[0013] The particle size of the pharmaceutically active compound in the nanosuspension may be in the range of 100 nm to 1000 nm, including all values and increments therein, such as in the range of 250 nm to 1,000 nm, etc. Illustrated in FIG. **1** is an exemplary embodiment of a numerical particle size distribution of suspension of TCO in PBS having a pH of 7.4 and at a concentration of 0.5 mg/mL. As can be seen in FIG. **1** the number percent particle size may range from 250 nm to approximately 1000 nm. In addition, the highest relative number percent of particles fall in the range of about 450-525 nm. Such particle size determination may be accomplished on a Beckman Coulter PCS Submicron Particle Size Analyzer. Accordingly, a nanosuspension herein may be understood as any liquid medium containing pharmaceutically active compounds having particles with a size of less than or equal to about 1000 nm.

[0014] The nanosuspensions formed herein may be optically clear or relatively transparent. This may be understood as a nanosuspension which is capable of transmitting about 85% or more visible light, including all values and increments therein. In addition, the nanosuspension may have a low refractive index in the range of 1.00 to 1.5 at a λ of 598.3 nm, including all values and ranges therein, such as 1.0003, 1.33, etc. The refractive index of the material may be understood as the ratio of the velocity of electromagnetic radiation in the nanosuspension relative to its velocity in a vacuum. Accordingly, attention may now therefore be directed to FIG. **2** which illustrates in diagram format certain particular features of the present disclosure identified above as applied to the formation of a nanosuspension herein containing a pharmaceutically active compound.

[0015] In a further embodiment secondary pharmaceutically active compounds may be added to the nanosuspension to increase the activity, bioavailability or absorption rate of the primary pharmaceutically active compounds. These secondary compounds may include those which increase tissue permeability and may be considered spreading or diffusing substances, such as hyaluronidase. Hyaluronidase may be understood as any group of enzymes that catalyze the hydrolysis of certain complex carbohydrates, including hyaluronic acid, chondroitin sulfates, etc. By hydrolyzing hyaluronic acid, for example, the primary pharmaceutically active compound may diffuse more readily through the tissue.

[0016] The pharmaceutically active compound may also be micro-encapsulated, which may be understood as a process in which relatively small particles or droplets are surrounded by a coating to give relatively small capsules with many useful properties. For example, the micro-encapsulate may be a relatively small sphere or core with a uniform wall around the sphere, which may be a coating, shell or membrane. The micro-encapsulate may be in the range of a few micrometers to a few millimeters. The nanosuspension may be released from the microcapsule by rupture, dissolution of the wall, melting of the wall and diffusion through the wall. The wall may be formed of a biodegradable or non-biodegradable materials. Such biodegradable materials may include polyglycolic acid, polylactic acid, polylactic-co-glycolic acid, polycaprolactone, polyanhydrides, polyesters, etc. Non-biodegradable materials may include polyethylene, polypropy-

lene, polyethylene-co-vinyl acetate, etc. The walls may be formed from a number of encapsulation processes such as coacervation, co-extrusion, interfacial polymerization, etc.

[0017] The following non-limiting examples provide further illustration regarding the formation of the pharmaceutically active nanosuspensions described herein.

EXAMPLE 1

[0018] A solution of TCO (1 mg) in hexafluoroisopropanol (HFIP) (0.5 mL) was prepared and added slowly into a magnetically stirred into phosphate buffered saline (PBS) (2 mL) having a pH of 7.4. The mixture was stirred uncovered in a fume hood for up to 24 hours. FIG. **2** illustrates the particle size distribution of suspension of TCO in pH 7.4 PBS at 0.5 mg/mL concentration. As illustrated in FIG. **2**, the particles are smaller than approximately 1,000 nm. The clear nanoparticle suspension was further concentrated in a vacuum oven to about 1.5 mg/mL. However, a 1.0 mg/ML nanosuspension by precipitating 2 mg/0.5 mL TCO/HFIP into 2 mL PBS resulted in a cloudy solution, indicating microparticles were formed instead.

EXAMPLE 2

[0019] A solution of TCO (1 mg) in hexafluoroisopropanol (0.5 mL) was prepared and added slowly into a magnetically stirred deionized water (2 mL). The mixture was stirred uncovered in a fume hood for 3 hours and further concentrated in a vacuum oven. The nanoparticle suspension in deionized water, however, could only be concentrated to about 0.6 mg/mL of concentration before growing micron-sized crystals.

[0020] Although the illustrative embodiments of the present disclosure have been described above with reference to the accompanying drawings and examples, it is to be understood that the disclosure is not limited to those precise embodiments, and various changes and modifications may be affected therein by one skilled in the art. It is intended that such changes and modifications be included within the scope of the appended claims.

What is claimed is:

1. A method for preparing a nanoparticulate suspension of a pharmaceutically active compound comprising:

combining a pharmaceutically active compound in a first solvent;

introducing said first solvent containing said pharmaceutically active compound into a second solvent and forming said nanoparticulate suspension;

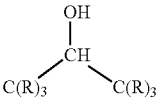
wherein said first and second solvent are substantially free of surfactant.

2. The method of claim **1** wherein the particle size of said pharmaceutically active compound in said nanoparticulate suspension is ≦1000 nm and said suspension is capable of transmitting ≧85% visible light.

3. The method of claim **2** wherein said particle size is between 250 nm-1000 nm.

4. The method of claim **1** wherein said first solvent is an organic solvent having a pKa≧7.0.

5. The method of claim **1** wherein said first solvent is an organic alcohol having the following general structure:



wherein one or more R groups comprise an electron-withdrawing group wherein the remaining R groups may comprise a hydrogen atom, an alkyl group, an aromatic group, a substituted alkyl group or a substituted aromatic group.

6. The method of claim **4** wherein one or more R groups is a halogen atom.

7. The method of claim **1** wherein said pharmaceutically active compound comprises a corticosteroid.

8. The method of claim **1** wherein said pharmaceutically active compound comprises triamcinolone, said first solvent comprises hexfluoroisopropanaol, and said second solvent comprises an aqueous medium.

9. A method for preparing a nanoparticulate suspension of a pharmaceutically active compound comprising:

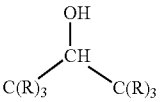
combining a pharmaceutically active compound in a first solvent;

introducing said first solvent containing said pharmaceutically active compound into a second solvent and forming said nanoparticulate suspension;

wherein said particle size of said pharmaceutically active compound in said nanoparticulate suspension is ≦1000 nm and said particle size is formed without mechanical shearing.

10. The method of claim **9** wherein said first solvent is an organic solvent having a pKa≧7.0.

11. The method of claim **9** wherein said first solvent is an organic alcohol having the following general structure:



wherein one or more R groups comprise an electron-withdrawing group wherein the remaining R groups may comprise a hydrogen atom, an alkyl group, an aromatic group, a substituted alkyl group or a substituted aromatic group.

12. The method of claim **11** wherein one or more R groups is a halogen atom.

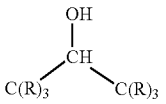
13. The method of claim **9** wherein said pharmaceutically active compound comprises a corticosteroid.

14. The method of claim **9** wherein said pharmaceutically active compound comprises triamcinolone, said first solvent comprises hexfluoroisopropanaol, and said second solvent comprises an aqueous medium.

15. The method of claim **9** wherein said first and second solvent are substantially free of surfactant.

16. A method for preparing a nanoparticulate suspension of a corticosteroid compound comprising:

combining a corticosteroid in a first organic solvent that is miscible with water wherein said solvent has the following general structure:



wherein one or more R groups comprise an electron-withdrawing group wherein the remaining R groups may comprise a hydrogen atom, an alkyl group, an aromatic group, a substituted alkyl group or a substituted aromatic group;

introducing said first solvent containing said pharmaceutically active compound into an aqueous medium and forming said nanoparticulate suspension;

wherein said first and second solvent are substantially free of surfactant wherein the particle size of said corticosteroid in said nanoparticulate suspension is ≦1000 nm, and said suspension is capable of transmitting ≧85% visible light.

17. A nanoparticulate suspension of a pharmaceutically active compound comprising:

pharmaceutically active compound particulate in a solvent at a particle size of ≦1000 nm, said suspension capable of transmitting ≧85% visible light and wherein said suspension is substantially free of surfactant.

18. The nanoparticulate suspension of claim **17** wherein said pharmaceutically active compound comprises a corticosteroid.

19. The nanoparticulate suspension of claim **17** wherein said surfactant is present at a level of ≦1.0 ppm.

20. The nanoparticulate suspension of claim **17** wherein said particle size is between 250 nm-1000 nm.

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